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Model of Cell Kinetics with Applications to the Acute Myeloblastic

Leukemic State in Man: Sol I. Rubinow, Graduate School of Medical Sciences, Cornell University, and Joel L. Lebowitz, Chmn. Dept. of Physics, Belfer Graduate School of Science, Yeshiva University.

We have developed [1] a mathematical model of neutrophil production and control in normal man. This model, while very simplified, was designed to incorporate all the known quantified kinetic parameters of granulocytogenesis. The model appears capable of describing in a semi-quantitative manner the consequences of various marrow precursor labelling experiments. It can also describe other experiments with mammals which strongly perturb the normal steady-state behavior of the production system, for example, by means of massive x-irradiation or other stresses that artificially induce a state of neutropenia. An important feature of the model is the existence of two feedback loops that control the rate of production of neutrophil precursors in the marrow, and the rate of release of mature non-proliferating marrow cells to the blood. These control elements homeostatically maintain the total number of neutrophils in the body at a prescribed level. When the system is perturbed, the model predicts a damped oscillatory return to equilibrium. Because of the nonlinear nature of the control system introduced, the return to equilibrium is accompanied by the phenomenon of "overshoot," which appears to be at least qualitatively consistent with the observed behavior of the response of the neutrophil system to such stress.

Our model was further extended [2] to describe the dynamic

properties of the neutrophil production system in the abnormal state of acute myeloblastic leukemia (AML). We adopted the point of view, advocated by Clarkson^[3] and others, that there exist side by side in AML two cell populations, the normal neutrophil cell system, and a leukemic cell population. In addition, we assume that the leukemic cell population system operates in a similar manner to the normal neutrophil population. Thus, each population is assumed to possess feedback control elements which regulate and control the total number of cells in the population. However, the leukemic cells are assumed to possess an aberrant set of kinetic parameters, different from those of the normal population. In other words, our fundamental point of view is that the leukemic state is not "uncontrolled growth," but rather, controlled growth with an abnormal set of control elements.

Thus, we assume that the control of proliferation is governed by the total population of the neutrophil system, including proliferative and non-proliferative cells. When there is a leukemic myeloblastic population coexisting with the normal population, we assume that both populations control their proliferative rate in response to the total population consisting of both normal and leukemic cells. This assumption provides a mechanism for the more or less sudden disappearance of the normal neutrophil population as the leukemic population approaches its stationary level. These latter characteristics of the natural history of the acute myeloblastic state constitute, in fact, the principal justification for the assumption.

We have superimposed on our model a drug treatment regimen [4],

which retains the essential rationale of the L-6 protocol used at the Sloan-Kettering Memorial Cancer Center in the chemotherapeutic treatment of patients with AML. It is assumed that the single administration of a drug dose results in the killing of a fixed fraction of all cells in S-phase, whether normal neutrophil precursors or leukemic myeloblasts. The period between successive drug doses, the number of doses in a course of treatment, the rest period between treatment courses, and the growth rate ('fast' or 'slow') of the leukemic cell population were varied in an attempt to determine the optimum regimen: one that maximizes the killing of the leukemic cell population and minimizes the killing of the normal cells.

Our calculations suggest that small changes in the protocol can have significant effects on the result of treatment. Thus, the optimal period between drug doses is the S-phase interval of the leukemic cells -- about 20 hrs., and the greater the number of doses administered in a given course treatment, the longer the rest interval should be before the next course is administered. For a patient with a 'slow' growing AML cell population, remission can be achieved with one or two courses of treatment, and further suppression of the leukemic population can be achieved with continued courses of treatment. However, for patients with a 'fast' growing AML cell population, a similar aggressive treatment regimen succeeds in achieving remission status only at the cost of very great toxic effects on the normal neutrophil population and

its precursors. The use of germ-free rooms and other support mechanisms in conjunction with chemotherapy will perhaps make such treatment regimens feasible in the future.

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